REMARKS

Claims 41, 42, 44-47, 49-56, 58, 59, 61-69 and 71-75 are pending. Claims 48, 57, 60 and 70 have been cancelled by way of this amendment.

No new matter has been added by way of the above amendments. For instance, new Claim 73 corresponds to the canceled Claim 70, in which the limitation concerning contacting the water-absorbing material is limited to a part or a pupil area of the ocular cornea, and the physical state of the water-absorbing material is defined as powder, gel, jelly or tablet. Please note that New Claim 74 corresponds to Claim 47, and New Claim 75 corresponds to Claim 45. Claims 44, 55 and 58 have also been amended. In Claim 44, the limitation concerning contacting the water-absorbing material is limited to a part or a pupil area of the ocular cornea, and Claim 48 is incorporated. In Claim 55, the limitation concerning contacting the water-absorbing material is limited to a part or a pupil area of the ocular cornea, and Claims 57 and 60 are incorporated. In Claim 58, a metal salt was deleted from the selection of the water-absorbing material. Additionally, claims 71 and 72, as well as new claim 73 (corresponding to claim 70) have inserted the phrase "wherein said difference in osmotic pressure produces corneal epithelial damage." Accordingly, no new matter has been added.

In view of the following remarks, Applicants respectfully

request that the Examiner withdraw all rejections and allow the currently pending claims.

Issues Under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 70-72 under 35 U.S.C. §112, second paragraph for the reasons recited at pages 2-3 of the outstanding Office Action. Applicants respectfully traverse.

Applicants have amended the relevant claims to include the phrase "wherein said difference in osmotic pressure produces corneal epithelial damage" as suggested by the Examiner. Accordingly, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Issues Under 35 U.S.C. §102(b)

The Examiner has rejected claims 44-48, 55-61 and 63 under 35 U.S.C. §102(b) as being anticipated by Gilbard et al., Ophthalmology (1984). Applicants respectfully traverse this rejection.

It is described on page 1207, right column lines 8-12 of Gilbard that:

> A conjunctival well, made by elevating the lids with subcutaneous sutures that were attached to elevated posts, was filled with a BSS solution such that the entire cornea was submerged. Baths were exchanged with fresh solution every hour.

Therefore, it is evident that Gilbard discloses that corneal

epithelial damage is formed on the entire cornea of a rabbit using a solution of metal salts.

In addition, the Examiner cites to Gilbard and asserts the following:

> Gilbard et al. teaches that results obtained using corneal explants in vitro are the same regardless of whether glucose or sodium chloride is used as the osmotic agent (paragraph bridging columns 1 and 2 on page 1208).

The portion of Gilbard cited by the Examiner simply infers that a solution of glucose can be used in place of a solution of metal salts. Even if the solution of glucose were similarly used, the corneal epithelial damage would be formed on the entire cornea of the rabbit.

On the other hand, in the animal recited in amended Claim 44 (and Claims 45-47 and 61 which depend therefrom) and amended Claim 55 (and Claims 56, 58, 59 and 63 which depend therefrom), the corneal epithelial damage is caused by contacting a part or a pupil area of the ocular cornea of the animal with a water-absorbing material used in the physical state of powder, gel, jelly or tablet. Therefore, in the animal, the corneal epithelial damage is formed in a part of the cornea.

As described above, since the shape of the corneal epithelial damage of the experimental animal of the present invention is clearly different from that of the rabbit of

Gilbard, the inventions as defined in amended Claims 44 and 55 are distinguishable from the disclosure of Gilbard. Accordingly, Applicants submit that no anticipation exists. The Examiner is therefore respectfully requested to withdraw this rejection.

Issues Under 35 U.S.C. §103(a)

The Examiner has also rejected claim 70 under 35 U.S.C. §103(a) as being obvious over Gilbard. The Examiner further rejects claims 64, 66, 67 and 69 under 35 U.S.C. §103(a) as being obvious over Yerxa in view of Gilbard and Fujihara. Applicants traverse these rejections.

Concerning the citation of Gilbard, Applicants submit that Gilbard neither discloses nor suggests the constitution of the present invention. Furthermore, especially remarkable effects can be exhibited in the present invention as follows. Specifically, the animal of the present invention has a corneal epithelial damage having uniform intensity of a desired size. For instance, when a pharmacological efficacy of a compound is evaluated using the animal, the evaluation can be made accurately by using an areal change of a damaged site as an objective index, and the evaluation can be made with the passage of time (page 18, lines 21-24 of the present specification).

Since the epithelial damage is formed by using the solution in the method of Gilbard, it would be difficult to control the size of the damaged site and to form uniform damage. Moreover, in

the method of Gilbard, since the solution of metal salts covers the entire surface of the eye of the animal, it is submitted that damage is also caused even in peripheral sites other than the cornea such as conjunctiva. If edema is caused by the damage, the surface area of the eye exposed to the external will likely be changed (reduced). Therefore, the animal obtained by Gilbard cannot exhibit the effects obtained by the present invention. Since the animal of the present invention cannot as a matter of course be obtained according to the method of Gilbard, the effects exhibited by the present invention cannot be anticipated therefrom. Therefore, the present invention is non-obvious over Gilbard.

Applicants note that claim 70 has now been cancelled, however, new claim 73 corresponds to cancelled claim 70. New claim 73 is non-obvious for the above reasons. Also, according to the method recited in claim 73, an experimental animal having specially remarkable effects, as recited in claims 44 and 55, can be obtained. Such effects are unexpected from Gilbard. Accordingly, new claim 73 is non-obvious over Gilbard.

Additionally, regarding claims 64, 66, 67 and 69, Applicants note that these claims relate to a screening method or evaluation method for a medicine using the animal recited in claim 44, old 45. Accordingly, these claims are allowable just as claims 44 and 55 are allowable. Reconsideration and withdrawal of this rejection is respectfully requested.

Applicants note that the Examiner has also pointed out, concerning claim 27 (corresponding to claim 64) and claim 38 (corresponding to claim 67) that

> "One would have a reasonable expectation of success in combining these teachings because the animal model of Gilbard can simply be substituted in method of Yerxa without modification of either teaching."

However, Applicants have found for the first time that the corneal epithelial damage can be caused by the use of a water-absorbing material in the physical state of powder, gel jelly or tablet. Since the references cited by the Examiner neither teach nor suggest this new finding, the model animal of the present invention cannot be obtained even when referred to these cited references. Therefore, one of ordinary skill in the art cannot arrive at the present invention simply by combining the cited references.

The method of the present invention uses a better animal for screening or evaluating a medicine as compared to that of Gilbard. For instance, the animal of the present invention can be prepared within 60 minutes, preferably within 20 minutes (page 18, lines 17-20 of the present specification).

It is described in the paragraph bridging the final column of page 1207 and the first column of page 1208 as follows:

> In six experimental trials BSS concentrated to 330, 360

> and 407 mOsm/L was used to bathe the ocular surface for separate 6- and 14-hour periods. In one trial with the 360 mOsm/L solution, a 4.5-hour trial replaced the 6-hour trial because the rabbit died prematurely.

In other words, in the method of Gilbard, since it takes at least 4.5 hours to cause the corneal epithelial damage in the animal, during which the animal is exposed to severe stress of anesthetics, there may be some cases where the animal dies during the treatment. As mentioned above, in the present invention, since the model animal can be prepared in a very short period of time, as compared to that of Gilbard, the length of exposure of the animal to stress by the anesthetic can be remarkable shortened. According to the present invention, the evaluation on pharmacological efficacy can be efficiently made in a short period of time without causing the animal to die during the preparation. In another aspect, such facts show that the method of the present invention is very excellent from the viewpoint of prevention of cruelty to animals as compared to any of the cited references.

Moreover, when the pharmacological efficacy of a compound is evaluated using the animal, the evaluation can be made accurately by using an areal change of a damaged site as an objective index, and the evaluation can be made with the passage of time. Such effects would not be exhibited even when the animal of Gilbard is used in the method of Yerxa in view of Fujihara, and the effects cannot be expected from these

references.

In summary, Applicants respectfully submit that the present claims define subject matter which is allowable over the cited art. Accordingly, the Examiner is respectfully requested to withdraw all rejections and allow the currently pending claims.

If the Examiner has any questions or comments, please contact Craig A. McRobbie, Registration No. 42,874 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Respectfully submitted,

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